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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,770	06/28/2007	Yoshihide Hayashizaki	1794-0190PUS1	5639

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EXAMINER	
KINGAN, TIMOTHY G	

ART UNIT	PAPER NUMBER
1797	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,770	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	TIMOTHY G. KINGAN	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to claim 1-19 and 24-26 have been considered but are moot in view of the new ground(s) of rejection. In consideration of amendments to the claims as well as the combination of the teachings found in the Hayashizaki and Beck references and what they would suggest to one of ordinary skill in the art, the previous indication of allowable subject matter (Claims 20-23) is withdrawn. However, examiner notes that the subject matter comprises means for atomizing and ionizing labeled biomolecules, taught by applicant's own prior art, together with means for correlating a signal from the mass spectrometer with that of a visual signal generated with radiation in the visible spectrum. Such combination of elements is known in the art as recited in the office action below.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. **Claims 1-6, 9, 11-15, 17-18 and 27** are rejected under 35 U.S.C. 103(a) as being unpatentable over Y. Hayashizaki and I. Tanihata, WIPO published patent application WO 2002/068952 (examiner relies on U.S. equivalent, U.S. Patent Application Publication 2004/0113606, herein after Hayashizaki) in view of K.M. Beck and D.S. Wunschel, U.S. Patent 6,680,477 (herein after Beck).

For Claims 1-6, 9, 11-15 and 18 Hayashizaki teaches performing laser ablation of polymers (biosamples or smear sample), with the use of ultra-short pulse laser beams, the polymers atomized to each of the atoms that constitute the polymer, with the atoms ionized into univalent ions followed by quantitative analysis of the ions generated by the ionization [0014]. Further, Hayashizaki teaches the polymers may be added with (labeled by) an elemental label (directly or indirectly labeling a substance) [0025], such label may be a stable isotopic label [0030] and that analysis may be performed on various kinds of polymers attached with elemental labels including DNA (nucleic acid), protein and PNA ([0013], [0135]) with use of a quadrupole mass spectrograph [0045], such as a time-of-flight mass spectrograph (analysis by mass spectrometry with a time-of-flight method). Hayashizaki also teaches that a probe comprising a nucleotide may be labeled with a stable isotope [0058], hybridized with target nucleic acid and laser ablated for analysis, thereby determining the quantity of the isotope contained in the hybridized probe [0059] (substance with a specific bond is labeled, bonded to probe by hybridization and analyzed for composition of labeled elements). Further Hayashizaki teaches that a plurality of probes may be labeled with different elements and simultaneously hybridized with the target to achieve multi-channeling capability when used with a DNA microarray (multi-channeling is conducted).

With regard to the step of moving the laser beams across different regions of the sample, Hayashizaki teaches moving the short pulse laser beam or the polymer, thereby performing ablation and analysis of different regions [0057]. Hayashizaki also teaches analyzing for composition of ionized elements, determining element strength

([0068], Figs. 3(a)-(c)), as well as morphological features of a sample region peeled off by irradiation, such step performed with use of a microscope ([0069], Fig. 4).

Hayashizaki does not specifically teach the step of generating an image which shows both a morphological characteristic and element strength. However, such step is known in the art. Beck teaches the step of multiple rastoring across a sample to form the pixels of an image comprising signal strength in mass spectra at X-Y locations from within a complex biological sample such as single cells, thereby allowing the assembly of an image detailing the two dimensional position for a particular m/z value (col 1, lines 37-48) (generating an image showing both a morphological characteristic, that is, distribution of signal, along with a signal strength). Further, applicant discloses that such step comprises an analysis conducted in the same style as a conventional in situ hybridization method [0113]. It would have been obvious to one of ordinary skill in the art to use the step of generating an image correlating signal strength with distribution in order to provide subcellular detail, for instance of nucleic acid targets, in organelles or regions such as the nucleus and the cytoplasm of a cell, thereby advancing a goal of mechanistic or functional significance of a target signal.

For Claim 17, Hayashizaki teaches laser beams of pulse duration of 1 femto second or more and 1 pico second or less, and a peak power of 1 gigawatt or more and 10 gigawatt or less [0032].

For Claim 27, Hayashizaki does not teach the step of displaying the strength of the elements on a screen. However, such elements are known in the art. Beck teaches a system for creating a correlated optical image of the ion desorption region of a sample

which comprises an image display unit (col 4, lines 51-62). It would have been obvious to one of ordinary skill in the art to use a display unit/screen for displaying the correlated image of Beck in the device of Hayashizaki and Beck in order to attain the convenience of imaging the sample, before and during data acquisition, thereby providing a means for positioning the source of irradiation in a selected portion of a larger sample for starting an experiment, as well as for providing readily available means commonly associated with a computer used for data acquisition and analysis, for displaying the results of an experiment.

3. **Claims 7 and 10** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki as applied to claim 2 above, and further in view of Y. Hayashizaki, WIPO published patent application WO 2002/044195. Examiner relies on U.S. equivalent, U.S. Patent Application Publication 2004/0115665 (herein after Hayashizaki '665).

For Claim 7, Hayashizaki does not teach use of labeled aptamers in analyzing molecules in a biosample. However, Hayashizaki teaches application of laser ablation to analysis of protein [0013], and Hayashizaki '665 teaches use of aptamers in analysis of proteins, such as thrombin [0005], such analysis comprising fixing of aptamer to a substrate/chip followed by binding of labeled ligand to said aptamer [0021]. From such teaching of binding of aptamer and labeled target, binding occurring in the solid phase, it would have been obvious to one of ordinary skill in the art, and with reasonable expectation of success, to label the aptamer for use in analysis of such binding event, in

order to provide the opportunity to screen libraries in a selection process characteristic of aptamers.

For Claim 10, Hayashizaki does not teach use of a labeled substance bonded by antigen-antibody reaction. However, Hayashizaki does teach the use of isotope-labeled protein in analysis of polymers [0135] and Hayashizaki '665 teaches that ligands may be detected by an antibody (protein) that specifically binds to the ligand [0068]. It would have been obvious to one of ordinary skill in the art, from the considerations on the use of proteins in labeling, according to Hayashizaki, and the specific types of proteins that may be employed in forming binding pairs, according to Hayashizaki '665, to use a labeled antibody for binding to its protein ligand in analysis, or the alternative labeling of the ligand protein in a binding event comprising its antibody, in order to attain the advantages in quantitative analysis and resolution, as taught by Hayashizaki.

4. **Claim 8** is rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki as applied to claim 3 above, and further in view of F. de Sauvage et al., U.S. Patent Application Publication 2003/0215457 (herein after de Sauvage).

For Claim 8, Hayashizaki does not teach labeling nucleic acid by a TUNEL method. However, such method of labeling nucleic acid (and use of such labeled material in applications comprising in situ hybridizations) is known in the art. de Sauvage teaches nick-end labeling of nucleic acids (TUNEL method) for use in hybridization studies and detection of cells undergoing apoptosis using tissue microarrays [0330]. It would have been obvious to one of ordinary skill in the art to use

TUNEL in labeling nucleic acids for use in hybridization studies in order to attain the advantage of use of a single method and label that may be applied in parallel to any number of target nucleic acids.

5. **Claims 19-26 and 28** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki in view of Beck.

For Claim 19-23, 25 and 26 Hayashizaki teaches an apparatus comprising an ultra-short pulse laser **20**, a focusing lens **22**, a target holder **14** and a quadrupole mass spectrometer 16 ([0083], Fig. 1) for performing ablation of polymers (biosamples or smear sample) with use of ultra-short pulse laser beams, the polymers atomized to each of the atoms that constitute the polymer, with the atomized elements then ionized into univalent ions followed by quantitative analysis of the atomic ions generated by the ionization [0014]. Further, Hayashizaki teaches the laser may be moved to permit changing the position of irradiation [0043], thereby permitting analysis effective for a DNA microarray (irradiate different regions of a biosample to be analyzed).

With regard to a microscope, Hayashizaki teaches observing a target from which a sample was peeled off by irradiation, such observation done with a microscope ([0069], Fig. 4) (a microscope for observing the shape of the biosample).

Hayashizaki does not specifically teach the step of generating an image which shows both a morphological characteristic and element strength; however, such step is known in the art. Beck teaches multiple rastoring across a sample to form the pixels of an image comprising signal strength in mass spectra at X-Y locations from within a

complex biological sample such as single cells, thereby allowing the assembly of an image detailing the two dimensional position for a particular m/z value (col 1, lines 37-48) (an image generating device to generate an image showing both a morphological characteristic and a signal strength). Further, applicant discloses that such step comprises an analysis conducted in the same style as a conventional in situ hybridization method [0113]. It would have been obvious to one of ordinary skill in the art to use such image generating device for correlating signal strength with distribution in order to provide subcellular detail, for instance of nucleic acid targets, in organelles or regions such as the nucleus and the cytoplasm of a cell.

Hayashizaki does not teach the elements of the microscope being an upright or inverted microscope, the objective arranged on the upper or lower surface of the biosample and the irradiation performed from the lower or upper surface of the sample. However, Beck teaches a system for focusing laser light for ionization in mass spectrometry coupled with a process for creating a correlated optical image of the ion desorption region of a sample (abstract), such system comprising a microscope objective for collecting light of an optical image of the sample receiving laser light for ionization, such image being recorded by a camera (col 7, lines 23-36) (imaging the position of a biosample corresponding to ablated spot by an image analysis apparatus). Further, Beck teaches that such microscope objective may be positioned above the slide (col 3, lines 47-48) or below a transparent slide (col 3, lines 49-51; Fig. 3), in the manner of an upright microscope with the objective for observation on the upper surface of the sample while also irradiating from the upper surface, as well as arranging the

objective on the lower surface for observation and irradiating from the lower surface, in the manner of an inverted microscope, providing for observation and irradiation through a single objective (meeting the limitations of Claims 21 and 23) and using a time of flight mass spectrometer for capturing and analyzing ions (col 7, lines 36-37). It would have been obvious to one of ordinary skill in the art to use the configurations of Beck in providing for arrangement of irradiation and imaging with the device of Hayashizaki in order to attain an optical pathway serving both irradiation and collection of image, thereby avoiding duplication of elements capable of serving both purposes.

Hayashizaki and Beck do not specifically teach limitations placing the microscope objective for morphological observation on the upper or lower surface while irradiating from the opposite surface. However, Beck teaches irradiation (and, therefore, observation) may be done through at least one confocal microscope objective (col 3, lines 1-7). Further, examiner notes that conventional upright microscopes provide a light source (irradiation) below the sample through the lenses of a condensor and an observation pathway above the sample through an objective, providing suggestion for the claimed configuration. In consideration of such teachings of Beck comprising the option of using more than one objective, an objective in a geometry which does not interfere with the path of desorbed sample ions (col 4, line 6-8), together with the known arrangement of irradiating and observing from opposite sides of a sample, it would have been obvious to one of ordinary skill in the art to use, and with reasonable expectation of success, an upright microscope with the objective on the upper surface while irradiating from the lower surface, or, reversing such elements, arranging the objective

on the lower surface while irradiating from above, as may be found in a conventional inverted microscope, in order to configure a system with separate optics for irradiation and observation, such functions most optimally served by optics incorporating features specific for the separate functions. Moreover, applicant has not disclosed a special advantage or criticality of one of these limited number of known arrangements. Finally, it would have been obvious to one of ordinary skill in the art to incorporate the ionization/imaging system, with a microscope objective, of Beck, with the laser and mass spectrometer of Hayashizaki in order to add the capability of analyzing the distribution of target molecules the capability of the device of Hayashizaki for analyzing the signal associated with target molecules.

For Claim 24, Hayashizaki teaches laser beams of pulse duration of 1 femto second or more and 1 pico second or less, and a peak power of 1 gigawatt or more and 10 gigawatt or less [0032].

For Claim 28, Hayashizaki does not teach a device for displaying the strength of the elements in different regions on a screen. However, such features are known in the art. Beck teaches a system for creating a correlated optical image of the ion desorption region of a sample which comprises an image display unit (col 4, lines 51-62). It would have been obvious to one of ordinary skill in the art to use a display unit/screen for displaying the correlated image of Beck in the device of Hayashizaki and Beck in order to attain the convenience of imaging the sample, before and during data acquisition, thereby providing a means for positioning the source of irradiation in a selected portion of a larger sample for starting an experiment, as well as for providing readily available

means, commonly associated with a computer that would be used for data acquisition and analysis, for displaying the results of an experiment.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. M. Stoeckli et al., Nature Medicine, vol. 7 (4) pp. 493-496, 2001. Stoeckli teaches imaging mass spectrometry (title), correlating the amount and distribution of ionizable biopolymers in tissue sections (morphological characteristic and element strength).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TGK /Jill Warden/
Supervisory Patent Examiner, Art Unit 1797